

## REMARKS/ARGUMENTS

In the Office Action mailed February 26, 2003, the tables were objected to. Claims 48-57 were rejected under 35 U.S.C. 101 as directed to non-statutory subject matter. Claims 48-57 were rejected under 35 U.S.C. 112, second paragraph. Claims 38-43, 48-53 and 104-106 were rejected under 35 U.S.C. 112, first paragraph. Claims 44-47 were allowed.

### Amendments

The tables on pages 35-38 have been cancelled and inserted as Figures 10-13. The specification has been amended to replace reference to the tables with reference to the new Figures. These amendments are supported by the specification as filed. Claims 48 and 54 have been amended to recite an isolated T cell. This amendment is supported by the specification as filed, for example page 4, lines 10-12. Independent claims 38 and 48 have been amended to specify the TCR has one or more mutations in a CDR. The amendments to claims 38 and 48 are supported by the specification as filed, including page 14, lines 16-18. Claim 40 and claim 46 have been amended to correct a typographical error. No new matter is added by any amendment.

### Objection to the Tables

In the Office Action mailed February 26, 2003, the tables on pages 35-38 of the specification were determined to be unsuitable for printing and were required to be canceled and resubmitted as Figures. In response, the tables on pages 35-38 have been cancelled and inserted as Figures 10-13. The Figure descriptions have been added to the specification and references to the Tables in the specification have been replaced with references to the Figures. These amendments are believed to overcome the objection.

### 35 U.S.C. 101 rejection

In the Office Action mailed February 26, 2003, claims 48-57 were rejected under 35 U.S.C. 101. The Office Action stated "claims 48-57 recite T cells expressing on their surfaces high affinity TCRs. The T cells are not claimed as being isolated or in vitro and so the claimed subject matter can read on T cells in vivo. The specification indeed contemplates that the T cells can be in vivo. The claims therefore can be read to include a human being containing the T cells because the claims read on cells making up a portion of a human being. Claims reading on human beings are non-statutory subject matter. Redrafting the claims to recite T cells in vitro or isolated T cells would be remedial."

In response, independent claims 48 and 54 have been amended as suggested by the Examiner to recite an isolated T cell. This amendment is believed to overcome the rejection.


35 U.S.C. 112, second paragraph rejection

In the Office Action mailed February 26, 2003, claims 48-57 were rejected under 35 U.S.C. 112, second paragraph. The Office Action stated "Applicants claim T cells expressing on their surfaces high affinity TCRs. The claims read on a T cell in an in vitro or in vivo environment. If the cell is present in an in vivo environment, the claims are vague in that the metes and bounds of the claimed subject matter are unclear. It is unclear if applicants are claiming a cell within a subject or the subject him or herself because the cell in an in vivo environment is a part of the subject."

In response, independent claims 48 and 54 have been amended to specify an isolated T cell. This amendment is believed to clarify that the cell is not present in an in vivo environment and is believed to overcome the rejection.

35 U.S.C. 112, first paragraph rejection

In the Office Action mailed February 26, 2003, claims 38-43, 48-53 and 104-106 were rejected under 35 U.S.C. 112, first paragraph. The Office Action states "Applicants claim soluble high affinity TCRs or T cells expressing high affinity TCRs exhibiting a dissociation constant for a given ligand (which can be a peptide/MHC ligand or a superantigen) of from about  $10^7$  to  $10^{10}M^{-1}$ . The claims read on a genus of soluble high affinity TCRs and T cells expressing high affinity TCRs directed against any antigens." The Office Action continues "applicants do not apparently disclose any specific soluble TCRs or T cells expressing TCRs on their surface which bind to ligands with the recited dissociation constants. No soluble TCRs or T cells expressing high affinity TCRs with the recited dissociation constants directed against a peptide/MHC ligand or a superantigen ligand are disclosed. . . . Given the absence of any disclosed examples of the recited invention and the absence of a disclosed or art recognized correlation between the structure of the recited TCRs and their function of binding to ligands with the recited dissociation constants, it must be considered that the skilled artisan would not conclude that applicants were in possession of the claimed genus."



- Independent claims 38 and 48 have been amended to specify the TCR has one or more mutations in a CDR. This amendment provides structural properties for the claimed TCRs.

One of ordinary skill in the art would recognize Applicants were in possession of the claimed invention by the description in the present specification. The invention claimed in the rejected claims is a soluble T cell receptor or T cell expressing on its surface TCRs having high affinity for a ligand exhibiting a dissociation constant for that ligand greater than about  $10^7 \text{ M}^{-1}$ , which TCR is a mutant TCR carrying one or more mutations in a CDR.

It is believed the written description requirement is satisfied in the present specification by sufficient description of a representative number of species by actual reduction to practice. Contrary to the statement in the Office Action, Applicants have provided examples of soluble TCRs and T cells expressing high affinity TCRs with the recited dissociation constants directed against a peptide/MHC ligand or a superantigen ligand. A number of mutants are specifically described that bind with the claimed affinity to a number of ligands. On page 18, lines 11-14, a soluble TCR having an affinity for the QL9/L<sup>d</sup> ligand of  $1.1 \times 10^8 \text{ M}^{-1}$  is described. In addition, on page 14, lines 16-20, TCR mutants are described having affinity of about  $1 \times 10^8 \text{ M}^{-1}$  for the p/MHC ligand. This actual reduction to practice describes a representative number of species and is believed to satisfy the written description requirement.

In addition, the present specification provides disclosure of relevant identifying characteristics (i.e., the structures described in the present specification) that show one of ordinary skill in the art would recognize applicant was in possession of the claimed invention at the time the application was filed. Table 1 (now Figure 10) gives the CDR sequences of 15 mutants prepared using the description of the invention. Table 2 (now Figure 11) gives the CDR sequences of mutants binding to the SIYR/K<sup>b</sup> ligand. The binding of the TCRs for the SIYR/K<sup>b</sup> ligand is described in the specification on page 32, lines 22-29. Table 3 (now Figure 12) gives the CDR sequences of mutant TCRs having high affinity for the dEV8/K<sup>b</sup> ligand. The binding of the mutant TCRs for the dEV8/K<sup>b</sup> ligand is described in the specification on page 33, lines 16-27. One of the mutant TCRs described in Figure 12 is also shown to bind to other ligands (page 33, line 29 through page 34, line 4, describing binding to three antibodies and an antigen). One of ordinary skill in the art would recognize methods for preparing mutant TCRs having one or more mutations in a CDR from Example 1 of the specification on pages 30 and 31. One of

ordinary skill in the art would recognize selection of high affinity TCR mutants having high affinity for different ligands from Examples 4 through 7 of the specification on pages 32 through 34. Mutant TCRs having one or more mutations in a CDR and the claimed dissociation constants are also shown in Figure 3 of the present specification, for example.

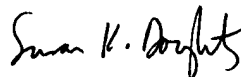
In view of the above arguments and amendments, claims 38-43, 48-53 and 104-106 are sufficiently described in the specification to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

### CONCLUSION

In view of the above arguments and amendments, it is believed all objections and rejections are overcome. Reconsideration and withdrawal of all objections and rejections is respectfully requested. If there are any further issues remaining to passage of the case to issuance, the Examiner is respectfully requested to telephone the undersigned.

It is believed that the present submission does not require the payment of any fees. If this is incorrect however, please charge any fees required, including any extensions of time required, or credit any overpayments to Deposit Account No. 07-1969.

Respectfully submitted,



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